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RESEARCH ARTICLE

Assessment of Auditory Pathways Using Diffusion Tensor Imaging in Patients with Neurofibromatosis Type 1

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Abstract: ***Aim*:** The aim of our study was to determine whether the diffusion properties of the auditory pathways alter between patients with Neurofibromatosis type 1 (NF1) and the healthy subjects. DTI can well demonstrate FA and ADC changes in auditory tracts and it may be a guide to identify the candidates for hearing loss among NF1 children.

***Methods*:** The study population consisted of 43 patients with NF1 and 21 healthy controls. Diffusion tensor imaging (DTI) was used to measure apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values from lemniscus lateralis, colliculus inferior, corpus geniculatum mediale and Heschl's gyrus. The results were compared with those of the control group.

***Results*:** The ADC values of lateral lemniscus, colliculus inferior and corpus geniculatum mediale were significantly higher in NF1 compared to those of the control group. On the other hand, decreased FA values were observed in lateral lemniscus and colliculus inferior in patients with NF1.

***Conclusion*:** The increase in ADC and reduction in FA in the auditory pathways of patients with NF1 may suggest microstructural alterations, such as a decrease in the number of axons, edema or inflammation in the auditory tracts.

Keywords: NF1, diffusion tensor imaging, Heschl's gyrus, colliculus inferior, mediale, corpus geniculatum.

1. INTRODUCTION

Neurofibromatosis (NF) is an autosomal dominant disease affecting various systems particularly the skin and the nervous system. Neurofibromatosis Type 1 (NF1) and Neurofibromatosis Type 2 (NF2) are two forms of the disease. NF2 which develops from a gene defect in 22nd chromosome, is characterized by peripheral and central nervous system tumors and a number of skin findings. NF1 develops from a gene defect of 17th chromosome. The incidence with 1/4000, NF1 is the disease involves several systems and organs in the body. Cafe au lait is a characteristic lesion of the skin and neurofibromas originate from nerve roots. Optic glioma, scoliosis, headache, epilepsy, learning difficulties, hearing loss, and cranial tumors are the complications [1-3]. While hearing loss is the basic symptom for NF2, it is also an important complication of NF1 [3].

Neuroradiologic imaging features are needed as much as clinical findings for the diagnosis of NF. Magnetic resonance imaging (MRI) is the method of choice for the diagnosis of central nervous system symptoms and tumors [1, 2]. Diffusion tensor imaging (DTI) is an advanced MRI method which demonstrates the connections between different brain regions and the integrity of the white matter tracts noninvasively. DTI is used to assess and digitize the diffusion properties of the white matter. It is also used to detect subtle changes in the brain tissue due to degeneration or injury and development [4-8]. The main measurements used in DTI are ADC (apparent diffusion coefficient) and FA (fractional anisotropy). ADC is an expression of the amount of diffusion and calculated by averaging all three eigenvalues in the tensor. FA quantifies the amount of anisotropic diffusion.

Auditory pathways are assessed with DTI in a few studies. As far as we know, NF1-related auditory pathway changes have not been studied. In this study, we evaluated diffusion changes in auditory pathways in NF1 patients compared with the control group.

2. MATERIALS AND METHODS

2.1. Patients

This retrospective study was approved by the institutional ethics committee. The study population consisted of 43 patients with NF1 (23 females and 20 males, the mean age±standard deviation (SD) 11.60±6.481 years, range 1-35) and 21 healthy controls (13 females and 8 males, with the mean age± SD 12.12±3.981 years, range 1-16).

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NF1 population consisted of patients who were previously diagnosed by a physician and referred to our radiology department for routine MRI examination between 2012 and 2017. The MR images of the patients were reviewed from the Picture Archiving and Communication System (PACS) of our hospital, and no new or additional imaging was needed. The control group that consisted of healthy people who were referred to our institution for brain MR imaging for other reasons, *e.g*. headache, and had normal MR findings was also selected from the PACS.

Exclusion criteria for both groups were systemic or cerebrovascular disease, head trauma, and degenerative changes in the brain tissue. ADC and FA values of lemniscus lateralis, colliculus inferior, corpus geniculatum mediale and Heschl's gyrus were measured in right auditory pathways.

2.2. MRI Technique

Patients with NF1 group and healthy controls were examined using a 1.5T MRI system (Siemens, Avanto, Erlangen, Germany) with a maximum gradient strength of 43 mT/m and an 18-channel head coil. Before performing DTI, the conventional MRI protocol included: three-dimensional magnetization-prepared rapid-acquisition gradient-echo T1-weighted (TR/TE/TI: 12.5/5/450ms; matrix 128x128), axial T2-weighted (TR/TE: 4.280/91 ms, matrix: 384x211, NSA: 1, slice thickness: 5mm) and T1-weighted (TR/TE: 500/87 ms, matrix: 256x125, NSA: 1, slice thickness: 5 mm), axial fluid-attenuated inversion-recovery (FLAIR) (TR/TE/TI: 8.000/118/23.687 ms, matrix: 256x140, NSA: 1, slice thickness: 5 mm), coronal FLAIR (TR/TE/TI: 8.000/118/23.695 ms, matrix: 256x144, NSA: 1, slice thickness: 5 mm), and T2-weighted sagittal (TR/TE: 4.810/90, matrix: 320x247, NSA: 1, slice thickness: 5 mm) images, and post-contrast axial, coronal, and sagittal T1-weighted (TR/TE: 86/476, matrix: 256x154, NSA: 1, slice thickness: 1 mm) images.

The DTI protocol included SE-EPI images, TR = 6.000 ms, TE = 89 ms, 30 gradient directions, b=0 s/mm^2 and b=1000s/mm^2, 5-mm slice thickness, FOV of 230 mm, and matrix: 128x128. FA and ADC maps were generated on a Leonardo console (software version 2.0; Siemens). A semi-automated system was used for DTI analysis. This was not a voxel-based, but the region of interest (ROI) based technique. The apparent diffusion coefficient (ADC) and color-coded fractional anisotropy (FA) maps were reconstructed on a Leonardo console (software version 2.0; Siemens) utilizing the DTI data. 3D T1 and T2-weighted images were used as anatomic references at the placement of the ROIs. These images were then matched with the corresponding regions in ADC and FA maps at the same anatomic level. The ROIs were drawn manually on axial colour-encoded FA maps in all subjects with simultaneous assessment of two experienced radiologists (A.A and S.A.) (Fig. **1**). Sizes of all ROIs were 4 pixels in lemniscus lateralis, colliculus inferior, corpus geniculatum mediale and Heschl's gyrus.

2.3. Statistical Analysis

Statistical analyzes were performed by using IBM SPSS Version 22.0. The Kolmogorov Smirnov test was used to determine whether the data corresponded to normal distribution. The Independent Samples t-test was used to compare normal independent variables. *P* values less than 0.05 were accepted as significant.

The power analysis was carried out by considering the variables to be measured in the study. At 80% power and 0.05 significance level, it was estimated that at least 15 subjects should be in each group.

3. RESULTS

FA and ADC values obtained from lemniscus lateralis, colliculus inferior, corpus geniculatum mediale and Heschl's gyrus in NF1 patients and the control group are shown at Table **1**. It took about 20-30 minutes per one subject to assess the prespecified areas, make measurements and record the data.

ADC values of lemniscus lateralis were significantly higher in NF1 group compared to healthy controls (P=0.01) (Fig. **2**). FA values in patients with NF1 were significantly lower in lemniscus lateralis (P<0.001) (Fig. **3**).

ADC values of colliculus inferior were significantly higher in NF1 patients compared to healthy controls (P<0.001) (Fig. **2**). FA values in patients with NF1 were significantly lower in colliculus inferior (P<0.04) (Fig. **3**).

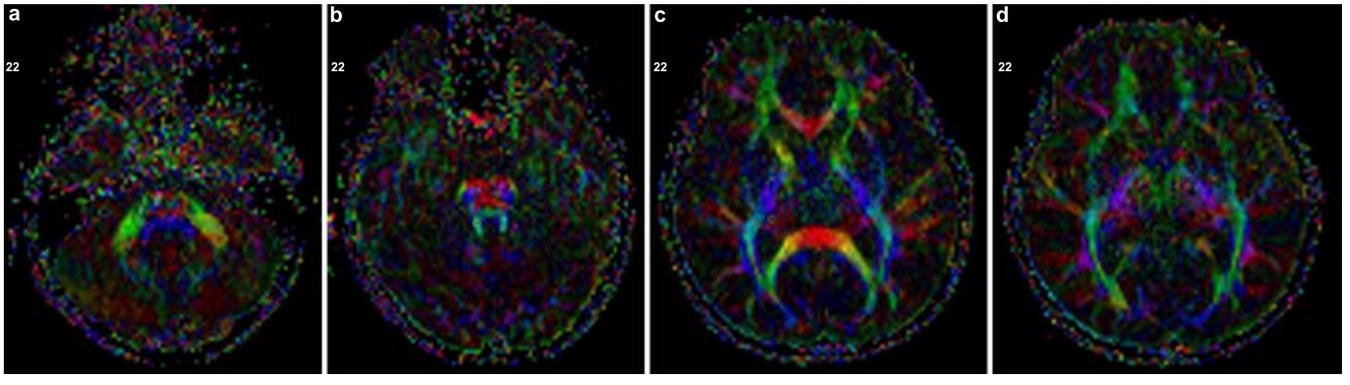

Fig. (1). The axial color-coded FA-maps at the level of the lateral lemniscus (**a**), inferior colliculus (**b**), corpus geniculatum mediale (**c**), and Heschl's gyrus (**d**) showing placement of regions of interest in a subject with NF1. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 1. The ADC and FA values obtained from the subjects with NF1 and the control group.

Locations	Lateral Lemniscus		Inferior Colliculus		Corpus Geniculatum Mediale		Heschl's Gyrus	
	ADC	FA	ADC	FA	ADC	FA	ADC	FA
NF1 (n:43)	850.7±110.1	570.8±112.3	863.7±88	641.66±91.6	864.3±99.5	354.8±109.9	864.3±83.1	283.4±103.3
Control (n:21)	793.6±64.9	662.8±74.9	768.7±85.6	681.87±57.6	807.7±62.6	360.8±85	848.9±63.1	250.7±44.5
P<(I *vs*. II)	0.01	<0.001	<0.001	0.04	0.01	NS	NS	NS

Results are presented as mean ± SD. SD: Standard Deviation; *NS:* Non Significant; *NF1:* Neurofibromatosis Type 1; *ADC*: Apparent Diffusion Coefficient; *FA*: Fractional Anisotropy.

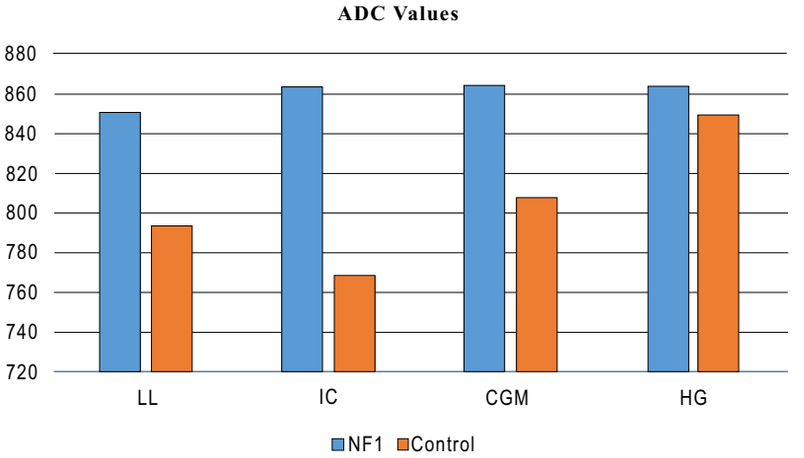

Fig. (2). The Apparent Diffusion Coefficient (ADC) values at the lateral lemniscus, inferior colliculus, corpus geniculatum mediale, and Heschl's gyrus of the subjects with NF1 compared with those of the control group.
NF1: Neurofibromatosis type 1, *LL*: Lateral Lemniscus, *IC*: Inferior Colliculus, *CGM*: Corpus Geniculatum Mediale, *HG*: Heschl's gyrus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

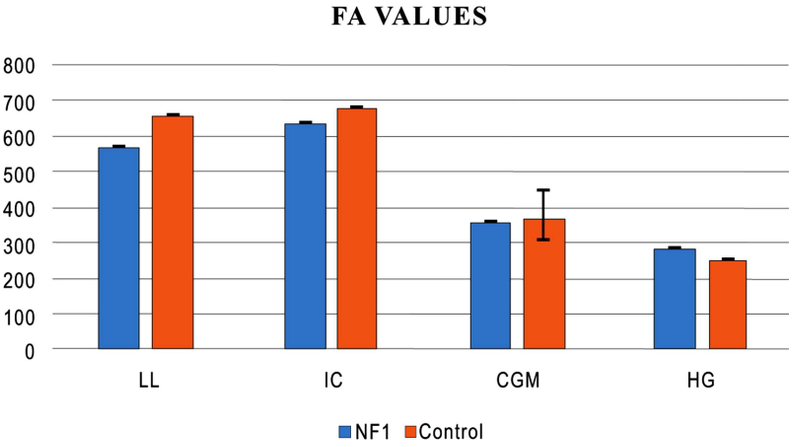

Fig. (3). The fractional anisotropy (FA) values at the lateral lemniscus, inferior colliculus, corpus geniculatum mediale, and Heschl's gyrus of the subjects with NF1 compared with those of the control group.
NF1: Neurofibromatosis type 1, *LL*: Lateral Lemniscus, *IC*: Inferior Colliculus, *CGM*: Corpus Geniculatum Mediale, *HG*: Heschl's gyrus. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ADC values of corpus geniculatum mediale were significantly higher in NF1 patients (*P*=0.01) (Fig. **2**). FA values in patients with NF1 were insignificantly lower in corpus geniculatum mediale (Fig. **3**).

ADC values of Heschl's gyrus were higher in NF1 patients. The increase in ADC values of Heschl's gyrus was statistically insignificant.

4. DISCUSSION

Cochlear nuclei are the first synapse sites in the brainstem for fibers of the 8th cranial nerve related to hearing function. The fibers derived from the cochlear nuclei make synaptic contacts with those of the contralateral formatio reticularis, nucleus olivarius superior and corpus trapezoide

nuclei. The postsynaptic fibers are called lemniscus lateralis. All of the fibers initiating from the cochlear nuclei are not crossed but a few of them ascend as ipsilateral lemniscus lateralis. These fibers then intermingle into the colliculus inferior, the center of hearing reflexes in the mesencephalon. The fibers initiating from colliculus inferior then reach to corpus geniculatum mediale and synapse here. The fibers that proceed after the synapse traverse through capsula interna under the name of radiatio acustica or tractus geniculotemporalis and reach to hearing center in the temporal lobe (Heschl's gyrus) [9]. In our study, we evaluated the unfavorable effects of NF1 in the anatomic regions mentioned above using DTI. DTI was used to find out diffusion changes comparatively in the NF1 patients and the control group by measuring of ADC and FA values.

There are a few studies on diseases involving the auditory pathways [3-6]. NF1 is one of these diseases. NF1 presents with neurocutaneous findings. It can involve peripheral nerves and eye as well as auditory pathways causing hearing loss [1-3]. Motor speech impairment, learning difficulties, reading, writing and expression difficulties are serious complications of the disease. NF1 patients are under the risk of hearing loss, deafness, and developing abnormal auditory brainstem responses [3].

In a study conducted on NF1 in 2014, FA and ADC values in gray and white matter were measured using DTI [10]. It was reported that ADC values were increased and FA values were decreased in NF1 cases compared to control. It has been suggested that increased ADC values may be related with increased extracellular fluid production and myelin sheath distribution due to decreased cellularity or number of axons [10]. Alkan *et al*. reported that frontal, parieto-occipital and cerebellar white matter and normal appearing basal ganglia structures in NF1 patients revealed increased ADC values [11]. Sheikh *et al*. attributed this increase to increasing number and/or size of myelin vacuoles [12]. Eastwood et al. suggested that children with NF1 might have a myelin disturbance, such as diminished myelin amount, increased myelin turnover, or demyelination, which causes expansion of the extracellular space and increase in ADC values [13]. Aydin *et al*. reported that there is a correlation between ADC and FA values measured in the genu of the corpus callosum and neurocognitive dysfunctions [14]. In a study on acoustic neuromas (AN), another disease that involves auditory pathways such as NF1, ADC increase was found in lateral lemniscus, colliculus inferior, corpus geniculatum mediale and Heschl's gyrus in AN patients when compared to healthy control subjects and thought to be related to microstructural changes such as dysmyelination or loss of myelin [4]. In another study of patients with sensorineural hearing loss, it was suggested that reduced FA values with increased radial diffusivity in the colliculus inferior and lateral lemniscus caused by the dysmyelination process [15]. In our study, we found that there was an increase in ADC values of the auditory pathways in patients with NF1. It is stated that the increased ADC values may be caused by any inflammation or edema or decreased number of axons and increased tissue fluid due to destruction of the myelin sheath [10, 16]. Therefore, we suppose that NF1 may lead to myelin sheath lesion, decreased axon number, edema and inflammation by causing increased ADC values. The Heschl's gyrus seemed to be less affected in our study. This was compatible with the course of the disease which involves cerebral deep white matter, basal ganglia and corpus callosum in the central nervous system. Decreased FA values were detected in colliculus inferior and lateral lemniscus. Additionally, there was statistically insignificant decrease in FA values in corpus geniculatum mediale and Heschl's gyrus. FA is a sensitive but nonspecific indicator of the microstructure of the white matter, and gives information about fiber density, axon diameter and myelination [14, 16]. In our study, decreased FA values in colliculus inferior and lateral lemniscus may be due to a decrease in fiber density or axon number and demyelination by changing microstructure in auditory pathways of patients with NF1.

Our study had some limitations. First, this was a retrospective study and sample size was relatively small. Secondly, we used a semi-automatic system to quantify the DTI data. With technical developments in this area, fully automated systems like tract-based spatial statistics (TBSS) have been presented. However, there is still no consensus on which approach is the best way to assess the tracts [17].

CONCLUSION

As a conclusion, our study demonstrated that neuronal integrity is affected by the auditory pathways in NF1, although symptoms related to hearing loss are infrequently observed in these patients. DTI is a recently developed MRI technique that provides quantitative information about the structural integrity of white matter tracts. It has been observed that the use of DTI in NF1 is an important diagnostic tool in this study. The increase in ADC and reduction in FA in the defined anatomic localizations may suggest microstructural alterations, such as decrease in the number of axons, edema or inflammation in the auditory tracts. Future longitudinal studies are needed to assess the clinical significance of auditory tract alterations in NF1. The augmentation of this work with other diffusion measures may clearify underlying mechanisms in more detail.

LIST OF ABBREVIATIONS

ADC	=	Apparent Diffusion Coefficient
DTI	=	Diffusion Tensor Imaging
FA	=	Fractional Anisotropy
MRI	=	Magnetic resonance imaging
NF1	=	Neurofibromatosis type 1
PACS	=	Picture Archiving and Communication System
ROI	=	Region of Interest
SD	=	Standard Deviation

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee for Non-Invasive Studies of the Bezmialem Vakif University (11375), Turkey.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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